

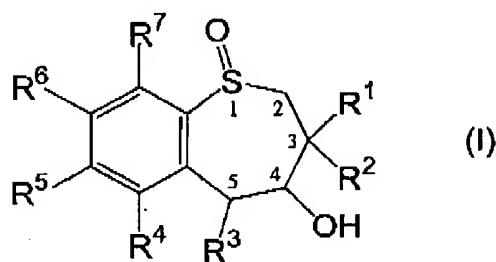
Jinglin Li *et al.*  
U.S. Patent Application Serial No. 10/072,600

Attorney Docket No. 161765.00465  
(3163/I/US/DIV)

This Listing of Claims will replace all prior versions, and listings, of claims in the application:

LISTING OF CLAIMS

1. (currently amended) A method of preparing an enantiomerically-enriched tetrahydrobenzothiepine-1-oxide having the formula (I):



wherein:

R<sup>1</sup> and R<sup>2</sup> are independently selected from the group consisting of H, alkyl, alkenyl, and alkynyl, cycloalkyl, aryl, and heteroaryl;

R<sup>3</sup> is selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, and cycloalkyl, heterocycle, quaternary heterocycle, OR<sup>15</sup>, SR<sup>15</sup>, S(O)R<sup>15</sup>, SO<sub>2</sub>R<sup>15</sup>, and SO<sub>3</sub>R<sup>15</sup>;

wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, and quaternary heteroaryl can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, and polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, halogen, oxo, OR<sup>19</sup>, NR<sup>19</sup>R<sup>20</sup>, SR<sup>19</sup>, S(O)R<sup>19</sup>, SO<sub>2</sub>R<sup>19</sup>, SO<sub>3</sub>R<sup>19</sup>, NR<sup>19</sup>OR<sup>20</sup>, NR<sup>19</sup>NR<sup>20</sup>R<sup>21</sup>, NO<sub>2</sub>, CO<sub>2</sub>R<sup>19</sup>, CN, OM, SO<sub>2</sub>OM, SO<sub>2</sub>NR<sup>19</sup>R<sup>20</sup>, C(O)NR<sup>19</sup>NR<sup>20</sup>, C(O)OM, COR<sup>19</sup>, P(O)R<sup>19</sup>R<sup>20</sup>, P<sup>+</sup>R<sup>19</sup>R<sup>20</sup>R<sup>21</sup>A<sup>-</sup>, P(O)R<sup>19</sup>OR<sup>20</sup>, S<sup>+</sup>R<sup>19</sup>R<sup>20</sup>A<sup>-</sup>, and N<sup>+</sup>R<sup>19</sup>R<sup>20</sup>R<sup>21</sup>A<sup>-</sup>;

— wherein

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A<sup>-</sup> is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation;  
 said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR<sup>13</sup>, NR<sup>13</sup>R<sup>14</sup>, SR<sup>13</sup>, S(O)R<sup>13</sup>, SO<sub>2</sub>R<sup>13</sup>, SO<sub>2</sub>R<sup>13</sup>, CO<sub>2</sub>R<sup>13</sup>, CN, exo, CONR<sup>13</sup>R<sup>14</sup>, N<sup>+</sup>R<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A<sup>-</sup>, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, P(O)R<sup>13</sup>R<sup>14</sup>, P<sup>+</sup>R<sup>13</sup>R<sup>14</sup>R<sup>15</sup>A<sup>-</sup>, and P(O)(OR<sup>13</sup>)OR<sup>14</sup>, and  
 wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR<sup>13</sup>, N<sup>+</sup>R<sup>13</sup>R<sup>14</sup>A<sup>-</sup>, S, SO, SO<sub>2</sub>, S<sup>+</sup>R<sup>13</sup>A<sup>-</sup>, PR<sup>13</sup>, P(O)R<sup>13</sup>, P<sup>+</sup>R<sup>13</sup>R<sup>14</sup>A<sup>-</sup>, or phenylene;

R<sup>19</sup>, R<sup>20</sup>, and R<sup>21</sup> are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl and aryl, arylalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroaryl, polyether, alkylarylalkyl, alkylheteroarylalkyl, alkylheteroalkyl, heterocycloalkyl, heteroarylalkyl, quaternary heteroalkyl, alkylammoniumalkyl, carboxyalkylaminocarbonylalkyl, and quaternary heteroarylalkyl,  
 wherein alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl optionally have one or more carbons replaced by O, NR<sup>15</sup>, N<sup>+</sup>R<sup>15</sup>R<sup>16</sup>A<sup>-</sup>, S, SO, SO<sub>2</sub>, S<sup>+</sup>R<sup>15</sup>A<sup>-</sup>, PR<sup>15</sup>, P<sup>+</sup>R<sup>15</sup>R<sup>16</sup>A<sup>-</sup>, P(O)R<sup>15</sup>, phenylene, carbohydrate, amino acid, peptide, or polypeptide, and

R<sup>19</sup>, R<sup>20</sup>, and R<sup>21</sup> are optionally substituted with one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, sulfoalkyl, carboxyalkyl, sulfoalkyl, alkyl, heterocycle, heteroaryl, quaternary heterocyclealkyl, quaternary heteroarylalkyl, guanidinyl, quaternary heterocycle, quaternary heteroaryl, OR<sup>15</sup>, NR<sup>15</sup>R<sup>16</sup>, N<sup>+</sup>R<sup>15</sup>R<sup>17</sup>R<sup>18</sup>A<sup>-</sup>, SR<sup>15</sup>, S(O)R<sup>15</sup>;

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~~SO<sub>2</sub>R<sup>15</sup>, SO<sub>3</sub>R<sup>15</sup>, exo, CO<sub>2</sub>R<sup>15</sup>, CN, halogen, CONR<sup>15</sup>R<sup>16</sup>, SO<sub>2</sub>OM, SO<sub>2</sub>NR<sup>15</sup>R<sup>16</sup>, PO(OR<sup>22</sup>)OR<sup>23</sup>, P<sup>+</sup>R<sup>15</sup>R<sup>16</sup>A<sup>-</sup>, S<sup>+</sup>R<sup>15</sup>R<sup>16</sup>A<sup>-</sup>, and C(O)OM,~~

~~wherein R<sup>22</sup> and R<sup>23</sup> are independently selected from the substituents constituting R<sup>15</sup> and M, or~~

~~R<sup>20</sup> and R<sup>21</sup>, together with the nitrogen atom to which they are attached, form a cyclic ring;~~

~~R<sup>24</sup> is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, alkylammoniumalkyl, and arylalkyl;~~

~~R<sup>13</sup> and R<sup>14</sup> are independently selected from the group consisting of hydrogen and alkyl;~~

~~R<sup>15</sup> and R<sup>16</sup> are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboalkylamino, heteroarylkyl, heterocyclealkyl, and alkylammoniumalkyl; and~~

~~R<sup>17</sup> and R<sup>18</sup> are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, OR<sup>15</sup>, NR<sup>15</sup>R<sup>16</sup>, SR<sup>15</sup>, S(O)R<sup>15</sup>, SO<sub>2</sub>R<sup>15</sup>, SO<sub>3</sub>R<sup>15</sup>, CO<sub>2</sub>R<sup>15</sup>, CN, halogen, exo, and CONR<sup>15</sup>R<sup>16</sup>, wherein R<sup>15</sup> and R<sup>16</sup> are as defined above, or~~

~~R<sup>17</sup> and R<sup>18</sup> together with the nitrogen or carbon atom to which they are attached form a cyclic ring; and~~

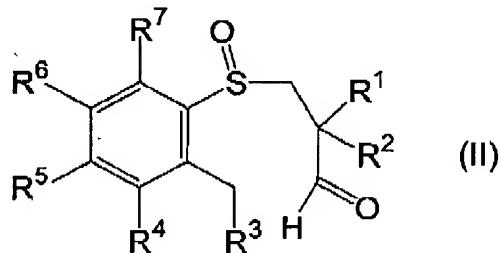
$R^4, R^5, R^6, R^7$  are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, halo, alkoxy, aryloxy, NO<sub>2</sub>, and -NR<sup>9</sup>R<sup>10</sup>;

$R^9$  and  $R^{10}$  are independently selected from the group consisting of H, and alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, butoxycarbonyl, and carbobenzoyloxy;

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R<sup>3</sup> and the hydroxyl at the 4-position of the enantiomerically-enriched tetrahydrobenzothiepine-1-oxide are in a syn-conformation with respect to each other; alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, alkoxy, and aryloxy can optionally be substituted with one or more moieties selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, alkoxy, aryloxy, NO<sub>2</sub>, and halo; and the sulfur at the 1-position of the seven-member ring and the carbons at the 4-position and the 5-position of the seven member ring are chiral centers; wherein the method comprises cyclizing an enantiomerically-enriched aryl-3-propanalsulfoxide having the formula (II):



wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, and R<sup>7</sup> are as described above, and wherein the sulfur is an enantiomerically-enriched chiral center, to form the enantiomerically-enriched tetrahydrobenzothiepine-1-oxide of formula (I).

Claims 2-64 (previously canceled).

65. (previously added) The method of claim 1, wherein said cyclizing step is performed in the presence of a base.

66. (previously added) The method of claim 65, wherein said base is potassium t-butoxide.